Remarks

Claims 1, 3-8, 10, 12-13, 19-24, 30, 32-33, 37 and 39 are pending after entry of the amendments set forth herein. Claims 2, 9, 11, 14-18, 25-29, 31, 34-36 and 38 are canceled without prejudice. Claims 3, 23, and 37 are amended. No new matter is added.

Claims 3, 23 and 37 have been rewritten in independent form, and Claim 33 has been amended to change its dependency to Claim 30. The amendments raise no new issues, and simplify the claim structure for allowance or appeal. Entry of the amendments is requested.

Rejections Under §112, ¶2

Claims 1, 3-8, 10, 12-13 and 19-24 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action states that Claim 1 is indefinite in the recitation of the term "does not substantially increase endothelial cell nitric oxide synthase activity", and suggests deletion of the term "substantially". Applicants respectfully submit that the phrase has been given a very specific meaning in the text of the specification at page 10, lines 2-6, which allows one of skill in the art to clearly understand the intended scope of the claim, and that to delete the word "substantially" would render the phrase without a clear meaning, as the definition provided by Applicants would then no longer be applicable.

In view of the above remarks, withdrawal of the rejection is requested.

Applicants note that for the purposes rejections made over the prior art reference Liao *et al.,* the present claims may be grouped separately.

Group I, Claim 1 and the claims dependent thereupon, i.e. Claims 4-8, 10, 12-13 and 19-22 are directed to methods of treating a lung proliferative disorder by administering an HMG-CoA reductase inhibitor.

Group II, Claim 3 is specifically directed to treating primary pulmonary hypertension in a patient.

Group III, Claim 23 and the claim dependent thereupon, i.e. Claim 24, are directed to methods of treating a primary pulmonary hypertension by administering an HMG-CoA reductase inhibitor by inhalation.

Group IV, Claim 30 and the claims dependent thereupon, i.e. Claims 32, 33, and 39 are directed to a method of reversing right ventricular hypertrophy in a patient suffering from pulmonary hypertension by administering an HMG-CoA reductase inhibitor.

Group V, Claim 37 is directed to methods of treating a primary pulmonary hypertension by administering simvastatin by inhalation.

Rejections Under §102

Claims 1, 3-8, 10, 12, 19-22, 30, 32-33 and 38-29 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Liao et al. (WO 00/56403). Applicants respectfully submit that the presently claims invention is novel in view of the cited art. It is noted that claim groups III and V are not included in this rejection.

The cited art, Liao *et al.*, describe a proposed method of treating various diseases by upregulating endothelial nitric oxide synthase (eNOS) activity in a subject. The requirement for upregulating eNOS is reiterated throughout the specification, for example at page 4, lines 23-26; page 6, lines 23-25, page 8, lines 5-7, page 5, lines 9-10, and in the claims, where it is specifically recited in, for example, Claims 1 and 5. It is therefore clear that the cited art intends a dose and route of administration of an HMG-CoA reductase that will result in increased eNOS activity.

Applicants further note that the cited art does not teach a method wherein this goal can be achieved in a patient suffering from a lung proliferative disorder. The reference provides the very general range of 0.1 mg/kg to 1000 mg/kg as being suitable for administration. However, the reference fails to provide any evidence that such a dose can be administered to an animal for the purpose of treating a lung proliferative disorder. The examples provided by Liao *et al.* relate to cell culture assays, for example as illustrated in Figures 1-3, which show changes in eNOS expression *in vitro*, or to cerebral infarction (Figures 4-6). There is no *in vivo* data provided by Liao *et al.* that would direct one of skill in the art in how to treat a lung proliferative disorder by administering an HMG-CoA reductase inhibitor in a dose that increases eNOS activity. While Liao *et al.* speculate and assert that this can be achieved; in fact there is no supporting evidence.

Applicants respectfully submit that the invention of groups I, II and IV, as set forth above, are not anticipated by the teaching of Liao *et al.* The invention of Groups I and II relate to the treatment of a lung proliferative disorder, particularly primary pulmonary hypertension, by administering an agent by a dose and route that does not substantially increase endothelial cell

nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient. Such a method is exemplified in the animal data provided by Applicants, for example as shown in Figures 1-12. While Liao *et al.* fail to provide a specific teaching of how the desired goal of their method can be achieved; it clearly cannot be the same as the methods taught by Applicants, since in one method eNOS expression is increased, and in the other method it is not substantially increased.

In view of the above, the Applicants contend that Claims 1, 3-8, 10, 12-13 and 19-22 are not anticipated by Liao *et al.* because Liao *et al.* fails to teach all the elements of the rejected claims and/or is not enabled with respect to the Applicants' claimed invention. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection be withdrawn.

Applicants wish to address the rejection of claim group IV separately. Applicants note that independent Claim 30 and dependent Claims 32, 33, and 39 are specifically directed to methods wherein there a reversal of right ventricular hypertrophy in a patient suffering from pulmonary hypertension.

Applicants respectfully submit that there is no mention or teaching of such a treatment in cited art. It is highly unexpected that one could achieve an actual reversal of existing disease, particularly of such a serious cardiac disorder. The cited art is completely silent on the subject, and the deficiencies of the art with respect to pulmonary proliferative diseases are even more noticeable on this point. Applicants respectfully submit that Liao *et al.* fail to teach the recited elements of the claimed invention. Withdrawal of the rejection is requested.

Rejections Under §103(a)

Claims 13, 23-24 and 36-37 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Liao *et al.* (WO 00/56403).

Applicants respectfully submit that the cited reference does not make obvious the presently claimed invention. For the reasons discussed above, Applicants respectfully submit that Liao *et al.* fail to teach a method wherein a pulmonary hyperproliferative disease that does not substantially increase endothelial cell nitric oxide synthase activity in the endothelial cells of the pulmonary arteries of the patient.

Applicants further note, as discussed above, that even for the methods claimed by Liao *et al.*, that is, a method wherein primary pulmonary hypertension is treated by administering an HMG-CoA reductase inhibitor in a dose that increases eNOS activity, the reference lacks

specific guidelines for dose and route of administration whereby one could accomplish the sought after result.

The Office Action states that "those of ordinary skill in the art would have been readily optimized effective delivery forms as determined by good medical practice and the clinical condition of the patient."

Applicants respectfully disagree. In view of this lack of teaching by the primary reference, it is not obvious that one should "optimize" effective delivery forms. The process of optimization lacks a credible foundation when the desired result has not yet been obtained, and becomes, instead, a searching for hope of success, without a reasonable expectation that such will be found.

Applicants respectfully submit that the invention of Groups III, (Claim 23-24) and Group V (Claim 37); and Claim 13 are not made obvious by the cited reference, Liao *et al.* Withdrawal of the rejection is requested.

Conclusion

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-352.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 19, 2007

By: _____
Pamela J. Sherwood
Registration No. 36,677

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231
F:\DOCUMENT\STAN(Stanford)\352\S01-118_STAN-352_Resp_to_FOA_filed_9-19-07.doc